REMARKS

Applicants respectfully request entry of the Amendment and reconsideration of the claims. Claims 1 and 6-16 are currently pending. Claims 1, 13, and 15 have been amended to add the treatment indication to the body of the claim. Support can be found throughout the specification, including at page 3, paragraph 10 and at page 13, paragraph 78. No new matter has been entered as a result of the amendment. Applicants respectfully request reconsideration and withdrawal of the pending rejection under 35 U.S.C. § 103(a).

Interview Summary

Applicants thank the Examiner for his time in discussing the pending claims during the recent interview at the U.S. Patent & Trademark Office on March 16, 2006. In attendance besides Examiner Jones were Dr. Albert Friesen and Dr. James Charlton of Medicure, Inc., and Dr. Ronald Daignault (Reg. No. 25,968). The Examiner and Dr. Friesen discussed pyridoxine's toxicity and ineffectiveness in treating cardiovascular related pathologies. In addition, the Examiner and Dr. Charlton discussed the difference between vitamin B_6 and vitamin B_6 derivatives in addition to clarifying the difference between therapeutically effective amounts of vitamin B_6 derivatives and nutritionally effective amounts to prevent vitamin deficiencies. This reply is drafted in keeping with the comments and discussion of the interview.

Rejection Under 35 U.S.C. §103(a)

The Examiner rejects the claims 1, 4-5, 7-12 and 14-16 under 35 U.S.C. § 103(a) as allegedly being unpatentable over pages 820-830 and 1562-1588 of Goodman & Gilman's The Pharmacological Basis of Therapeutics (9th Ed.)in view of U.S. Patent No. 3,282,778 (Lobel). Specifically, the Examiner states

> ...one having ordinary skill in the art would have been motivated to administer as well as be motivated to maintain healthy diets, through intake and supplemental aids, such as the administration of a multi-vitamin and lower salt intake.
> Office Action, Sept. 26, 2005 at p. 4.

Applicants respectfully traverse the rejection.

To establish a *prima facie* case of obviousness, three criteria must be met--a suggestion or motivation to combine references, a reasonable expectation of success, and the prior art

reference teaches or suggests all the claim limitations. MPEP § 2143; *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). Pyridoxine is distinct from pyridoxal-5'-phosphate, pyridoxal, pyridoxamine, and 3-acylated pyridoxal analogues. Administration of a therapeutically effective amount pyridoxine has been both toxic and ineffective in treating cardiovascular pathologies. Applicants respectfully assert that the Examiner has not sufficiently established a motivation to combine references.

Cited Art. The Examiner cites a general pharmacological textbook, Goodman & Gilman's The Pharmacological Basis of Therapeutics, to recite the various cardiovascular therapeutic compounds known at the time of filing. In addition, the Examiner cites Goodman & Gilman's for disclosing pyridoxine and pyridoxine derivatives. The Examiner combines this general pharmacological textbook with U.S. Patent No. 3,282,778 (Lobel). Lobel discloses using pyridoxine and pyridoxine derivatives as a vehicle for administering aspirin (acetyl salicylic acid) and bufferin (acetyl salicylic acid with aluminum glycinate) and producing a synergistic effect of the medicine. Although there is no support, Lobel recites using pyridoxine and pyridoxine derivatives as a vehicle to increase the effect and rapidity of absorption of a long list of various drugs, including cardiovascular drugs (Col. 1, ll. 18-29). Applicants respectfully assert that Lobel does not provide support for using pyridoxine derivatives. Lobel's experiments only utilized pyridoxine hydrochloride and not any pyridoxine derivatives. As discussed below in further detail, pyridoxine is pharmaceutically distinct from pyridoxal-5'-phosphate and other pyridoxine derivatives in safety, pharmacodynamics, pharmacokinetics and bioavailability.

Upon closer inspection, Lobel does not even provide objective evidence that the combination provided greater results than aspirin or bufferin alone. Lobel only administered aspirin or bufferin in combination to pyridoxine to those patients diagnosed with both coryza and rhinitis while patients only diagnosed with coryza received aspirin or bufferin alone (See Table 1 at col. 3, ll. 8-28). Additionally, all of the therapeutics were given *pro re nata* (prn). Therefore, the therapeutics were taken at the discretion of the patient. There appears to be no standardization to this study. Applicants respectfully assert that Lobel's disclosure does not support the combination of pyridoxal-5'-phosphate and pyridoxine derivatives with therapeutic cardiovascular compounds.

Pharmaceutically Distinct. Although there are metabolic pathways from all of the vitamin B_6 precursors to pyridoxal-5'-phosphate, they are not pharmaceutically equivalent. These differences apply to safety, pharmacodynamics, pharmacokinetics and bioavailability. For instance, published reports indicate that doses of pyridoxine over 25 mg produce little change in plasma pyridoxal-5'-phosphate levels (Ubbink *et al*, 1987). Thus it is impossible that therapeutic plasma levels of pyridoxal-5'-phosphate could be obtained through oral pyridoxine supplementation. In terms of pharmacodynamics, pyridoxal-5'-phosphate is likewise differentiated from vitamin B_6. For example, *in vitro* experiments comparing the antioxidant activity of different B_6 derivatives demonstrated that pyridoxal-5'-phosphate had significantly greater antioxidant activity than did pyridoxine (Chumnantana *et al*, 2005). Similarly, *in vitro* experiments comparing the ability of different B_6 derivatives to prevent lipid peroxidation demonstrated that pyridoxal-5'-phosphate significantly reduced lipid peroxidation, whereas pyridoxine did not (Kannan *et al*, 2004). In a study comparing the ability of pyridoxine, pyridoxamine, pyridoxal and pyridoxal-5'-phosphate to prevent lipid glycation in an *in vitro* model, pyridoxal-5'-phosphate and pyridoxal performed significantly better than pyridoxine (Higuchi *et al*, 2006). Clinically, pyridoxal-5'-phosphate has been found to alleviate epileptic seizures which do not respond to treatment with pyridoxine (Kuo *et al*, 2002; Wang *et al*, 2005). In view of the foregoing, pyridoxal-5'-phosphate and pyridoxine derivatives are distinct from pyridoxine.

Dosages of pyridoxine produce neurotoxicity when administered at the therapeutically effective amounts of claimed pyridoxine derivatives (Schaumberg et al., 1983, *N. Eng. Med. J.*; Bässler, 1988, *Internat. J. Vit. Nutr. Res.*; Holman, 1995, *J. Austral. Coll. Nutr. Environ. Med.*). In view of pyridoxine's neurotoxicity, the art as a whole teaches away from administering pyridoxine at therapeutically effective amounts. "A reference may be said to teach away when a person of ordinary skill, upon [examining] the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). If one was to extrapolate pyridoxine to pyridoxal-5'-phosphate and the other claimed compounds, one would also assume that a therapeutically effective dose would be toxic. However, pyridoxal-5'-phosphate has been therapeutically administered (both orally and parenterally) at dose levels up

to 50 mg/kg/day to children with West syndrome and related disorders, with no treatment-related neurological findings or other major adverse findings reported (Hirai *et al*, 1998; Seki, 1990; Ohtsuka *et al*, 1987). Applicants respectfully assert that there is no motivation to combine the references in view of the art demonstrating neurotoxicity to arrive at the claimed subject matter.

Nutritional vs. Therapeutic. Additionally, not all of the claim limitations (e.g., "a therapeutically effective amount") have been taught or suggested by the cited art. A nutritionally effective amount of vitamin B_6 is distinct from the disclosed therapeutically effective amounts of pyridoxal-5'-phosphate and other vitamin B_6 derivatives used to treat the indications disclosed in the instant specification (See table at S-12, "Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline"). In view of pyridoxine's neurotoxicity at therapeutically effective amounts, there is no teaching or suggestion of a therapeutically effective amount. The cited art only discusses pyridoxine at amounts to correct nutritional deficiencies. Since pyridoxine is toxic at higher dosages, there is not even a suggestion of therapeutically effective amounts of pyridoxine. Additionally, pyridoxine is not claimed and, as discussed above, is distinct from pyridoxal-5'-phosphate, pyridoxal, pyridoxamine, and 3-acylated pyridoxal analogues. Hence, the cited art does not teach nor suggest all of the instant claim limitations.

Additionally, the indication in the instant claims, congestive heart failure, is not associated with a vitamin deficiency. Hypertrophy is the result of myocyte increases in size due to pressure or volume overload or trophic signals and not due to a vitamin deficiency. None of the cited art recites or suggests that pyridoxine derivatives would treat hypertrophy. In fact, recent studies have demonstrated that pyridoxine does not prevent myocardial infarction or cerebral vascular accidents, nor does pyridoxine produce beneficial effects in subjects at high risk for cardiovascular events. Thereby the Examiner has not established that the two compositions (a therapeutic cardiovascular compound and the claimed pyridoxine derivatives) are taught by the prior art to be useful for the same purpose. Applicants respectfully assert that the Examiner has not established a motivation to combine the cited art to arrive at the claimed subject matter or a reasonable expectation of success.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection under § 103(a).

Summary

In view of the above amendments and remarks, Applicants respectfully requests a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,

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Date: March 24, 2006

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